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L1: Entry 6 of 9 File: USPT Sep 12, 2000

DOCUMENT-IDENTIFIER: US 6117642 A
TITLE: Methods of determining disease activity in SLE patients by correlating the level of soluble CD40 ligand

DRPR:
FIGS. 4A-4L are graphic illustrations of fluorescence-activated cell sorting (FACS) analysis of CD40L expression on purified B cells that were obtained from 12 different patients suffering from chronic lymphocytic leukemia (CLL). CD40L expression is indicated by the black line. Background immunofluorescence, defined using an irrelevant monoclonal antibody, is shown by the shaded area.

DRPR:
FIGS. 11A-C are graphic illustrations of FACS analysis of the induction of Fas (CD95) expression by sCD40L. Ramos B cells derived from a patient with Burkitt's lymphoma were incubated for 48 hours with culture medium alone ("medium"), with supernatant from 293 cells transfected with CD40L ("293-CD40L"), or with supernatant from 293 cells expressing CD8 ("293-CD8"). Fas expression was measured by direct immunofluorescence using a fluorescein-labeled anti-Fas antibody. The percentage of cells that were determined to be Fas-positive is indicated on each histogram.

DEPR:
The experiments described below were performed to determine whether soluble CD40L induces expression of activation antigens, such as, e.g., the Fas antigen, on target cells. Ramos B cells, derived from a patient with Burkitt's lymphoma, were incubated for 48 hours with culture medium alone, with supernatant from 293 cells expressing CD40L, or with supernatant from 293 cells expressing CD8. Fas (CD95) expression was measured on the Ramos B cells by flow cytometry using a fluorescein-labeled anti-CD40L antibody.

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L1: Entry 8 of 9 File: USPT Mar 2, 1999

DOCUMENT-IDENTIFIER: US 5876950 A
TITLE: Monoclonal antibodies specific for different epitopes of human GP39 and methods for their use in diagnosis and therapy

ABPL:
The present invention provides monoclonal antibodies, antigen binding fragment and recombinant binding proteins specific for human gp39. These antibodies are specific for at least eight different epitopes on gp39. Hybridomas secreting specific antibodies which bind to these epitopes are also provided. Further, the present invention discloses the amino acid sequence of immunoglobulin light and heavy chain variable regions which bind to epitopes of gp39 and provide sFv and humanized antibodies which bind gp39. Also, provided are pharmaceutical compositions comprising the monoclonal antibodies, antigen binding fragments and recombinant binding proteins which bind gp39 and methods for using these compositions in diagnosing disease states, inhibiting B cell activation and for treating immunological disorders, such as autoimmune diseases, allergic responses, organ rejection and graft-versus-host disease. Antibodies of the present invention can also be used to image cells which express gp39 on their surface, such as tumor cells (e.g., lymphoma) and to target therapeutic agents to target cells.

WEST

End of Result Set

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L1: Entry 9 of 9 File: USPT Oct 7, 1997

DOCUMENT-IDENTIFIER: US 5674492 A
TITLE: Method of preventing or treating disease characterized by neoplastic cells expressing CD40

BSPR:
Garnier et al. observed that antibodies to CD40 or another B cell marker, CD23, showed some degree of effectiveness at inhibiting lymphoma formation in SCID mice that had been injected with human PBL and then infected with EBV (Abstract 167, XIVth Intl. Congress of the Transplantation Society, 1992). However, it was unknown in the art whether the mechanism of action involved was inhibition of binding of CD40L to CD40 by the anti-CD40 antibody, or by some other means. Therefore, there is a need in the art to determine the effects of other anti-CD40 antibodies, and of CD40L itself, upon B cell lymphomas and other malignant cells that express CD40.

BSPR:
The present invention relates to a method of treating a mammal afflicted with a disease characterized by neoplastic cells that express CD40, comprising administering a therapeutically effective amount of a CD40 binding protein in a pharmaceutically acceptable buffer. The therapeutically effective amount is from about 0.01 to about 1 mg/kg body weight. CD40 binding proteins may be selected from the group consisting of monoclonal antibodies to CD40, CD40 ligand, and combinations thereof. Particularly preferred monoclonal antibodies are HuCD40-M2 (deposited at the American Type Culture Collection, 12301 Parklawn Dr., Rockville, Md., 20852, USA, under the terms of the Budapest Treaty, and given ATCC accession number HB11459) and HuCD40-M3, which are described in U.S.S.N. 08/526,014, filed Sep. 8, 1995, now pending, a continuation of U.S.S.N. 08/130, 541, filed Oct. 1, 1993, now abandoned. Oligomeric forms of CD40 ligand are particularly preferred, and include a soluble CD40 ligand-Fc fusion protein, and an oligomeric CD40 leucine zipper fusion protein, both of which have been described in U.S.S.N. 08/477,733, filed Jun. 7, 1995, now pending, and U.S.S.N. 08/484,624, filed Jun. 7, 1995, now pending, both of which are continuations in part of U.S.S.N. 08/249,189, filed May 24, 1994, now pending, which is a continuation in part of U.S.S.N. 07/969,703, filed Oct. 23, 1992, now abandoned. The present invention also relates to a method of preventing a disease characterized by neoplastic cells that express CD40, in a mammal susceptible to the disease, comprising administering a therapeutically effective amount of a CD40 binding protein in a pharmaceutically acceptable buffer, wherein the therapeutically effective amount is from about 0.01 to about 1 mg/kg body weight. Neoplastic cells that express CD40 include B lymphoma cells, some melanoma cells and some carcinoma cells.

DEPR:
Exemplary results are presented in FIG. 4; values are presented as percent of inhibition compared to control supernatant fluids. The soluble human ligand was inhibitory for the various lymphomas tested, with maximal inhibition seen (50-80%) on RL and TU2C cell lines at a 1:5 dilution of the supernatant fluid. The soluble murine CD40L produced similar, if not better, inhibitory effects. Control supernatant fluid from COS-7 cells transfected with vector alone actually promoted lymphoma cell growth. Accordingly, the inhibitory effects of CD40L on B lymphomas parallels that of antibodies to CD40.

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Search Results - Record(s) 1 through 9 of 9 returned.

☐ 1. Document ID: US 20010018041 A1

L1: Entry 1 of 9 File: PGPB Aug 30, 2001

PGPUB-DOCUMENT-NUMBER: 20010018041
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010018041 A1

TITLE: Treatment of B cell malignancies using anti-CD40L antibodies in combination with anti-CD20 antibodies and/or chemotherapeutics and radiotherapy

PUBLICATION-DATE: August 30, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hanna, Nabil	Rancho Santa Fe	CA	US	
Hariharan, Kandasamy	San Diego	CA	US	

US-CL-CURRENT: 424/1.49; 424/181.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 6312693 B1

L1: Entry 2 of 9 File: USPT Nov 6, 2001

US-PAT-NO: 6312693
DOCUMENT-IDENTIFIER: US 6312693 B1

TITLE: Antibodies against human CD40

DATE-ISSUED: November 6, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Aruffo; Alejandro A.	Belle Mead	NJ	08502	
Hollenbaugh; Diane	Newtown	PA	18940	
Siadak; Anthony W.	Seattle	WA	98107	
Berry; Karen K.	Princeton	NJ	08540	
Harris; Linda	Seattle	WA	98112	
Thorne; Barbara A.	Issaquah	WA	98029	
Bajorath; Jurgen	Lynnwood	WA	98037	
Huse; William D.	Del Mar	CA	92014	
Wu; Herren	San Diego	CA	92130	
Watkins; Jeffry D.	Encinitas	CA	92024	

US-CL-CURRENT: 424/154.1; 424/130.1, 424/133.1, 424/141.1, 424/143.1, 424/173.1, 435/252.2, 435/320.1, 435/326, 435/328 , 435/332, 435/334, 435/343, 435/343.1, 435/455, 435/471, 435/69.6, 530/387.1, 530/387.3, 530/388.1, 530/388.2, 530/388.22, 530/388.7, 530/388.73, 536/23.1, 536/23.5, 536/23.53

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 3. Document ID: US 6214562 B1

L1: Entry 3 of 9 File: USPT Apr 10, 2001

US-PAT-NO: 6214562
DOCUMENT-IDENTIFIER: US 6214562 B1

TITLE: Transcriptionally regualted G protein-coupled receptor

DATE-ISSUED: April 10, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Weng; Zhigang	Cambridge	MA		
Witte; Owen N.	Sherman Oaks	CA		

US-CL-CURRENT: 435/7.1; 435/252.3, 435/325, 435/456, 435/69.1, 435/7.2, 435/7.21, 536/23.1, 536/24.3

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 4. Document ID: US 6207412 B1

L1: Entry 4 of 9 File: USPT Mar 27, 2001

US-PAT-NO: 6207412
DOCUMENT-IDENTIFIER: US 6207412 B1

TITLE: Identification of a G protein-coupled receptor transcriptionally regulated by protein tyrosine kinase signaling in hematopoietic cells

DATE-ISSUED: March 27, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Weng; Zhigang	Los Angeles	CA		
Witte; Owen N.	Sherman Oaks	CA		

US-CL-CURRENT: 435/69.1; 435/252.3, 435/320.1, 435/325, 536/23.1, 536/24.31

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. Desc | Image

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☐ 5. Document ID: US 6197584 B1

L1: Entry 5 of 9 File: USPT Mar 6, 2001

US-PAT-NO: 6197584
DOCUMENT-IDENTIFIER: US 6197584 B1

TITLE: Antisense modulation of CD40 expression

DATE-ISSUED: March 6, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bennett; C. Frank	Carlsbad	CA		
Cowsert; Lex M.	Carlsbad	CA		

US-CL-CURRENT: 435/366; 435/325, 435/375, 435/6, 536/23.1, 536/24.31, 536/24.33, 536/24.5

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. Desc | Image

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☐ 6. Document ID: US 6117642 A

L1: Entry 6 of 9 File: USPT Sep 12, 2000

US-PAT-NO: 6117642
DOCUMENT-IDENTIFIER: US 6117642 A

TITLE: Methods of determining disease activity in SLE patients by correlating the level of soluble CD40 ligand

DATE-ISSUED: September 12, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Crow; Mary K.	New York	NY		
Vakkalanka; Radha Krishna	New York	NY		

US-CL-CURRENT: 435/7.1; 436/501, 436/506, 436/536

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 7. Document ID: US 6051228 A

L1: Entry 7 of 9 File: USPT Apr 18, 2000

US-PAT-NO: 6051228
DOCUMENT-IDENTIFIER: US 6051228 A

TITLE: Antibodies against human CD40

DATE-ISSUED: April 18, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Aruffo; Alejandro A.	Belle Mead	NJ		
Hollenbaugh; Diane	Newtown	PA		
Siadak; Anthony W.	Seattle	WA		
Berry; Karen K.	Princeton	NJ		
Harris; Linda	Seattle	WA		
Thorne; Barbara A.	Issaquah	WA		
Bajorath; Jurgen	Lynnwood	WA		

US-CL-CURRENT: 424/144.1; 424/130.1, 424/133.1, 424/141.1, 424/143.1, 424/153.1, 424/173.1, 435/252.3, 435/320.1, 435/452, 530/387.1, 530/387.3, 530/388.2, 530/388.22, 530/388.7, 530/388.73, 536/23.53

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 8. Document ID: US 5876950 A

L1: Entry 8 of 9 File: USPT Mar 2, 1999

US-PAT-NO: 5876950
DOCUMENT-IDENTIFIER: US 5876950 A

TITLE: Monoclonal antibodies specific for different epitopes of human GP39 and methods for their use in diagnosis and therapy

DATE-ISSUED: March 2, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Siadak; Anthony W.	Seattle	WA		
Hollenbaugh; Diane L.	Seattle	WA		
Gilliland; Lisa K.	Bellevue	WA		
Gordon; Marcia L.	Seattle	WA		
Bajorath; Jurgen	Lynnwood	WA		
Aruffo; Alejandro A.	Edmonds	WA		

US-CL-CURRENT: 435/7.23; 424/133.1, 424/135.1, 424/144.1, 424/154.1, 435/343.2, 435/7.24, 530/387.3, 530/388.75

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

☐ 9. Document ID: US 5674492 A

L1: Entry 9 of 9 File: USPT Oct 7, 1997

US-PAT-NO: 5674492
DOCUMENT-IDENTIFIER: US 5674492 A

TITLE: Method of preventing or treating disease characterized by neoplastic cells expressing CD40

DATE-ISSUED: October 7, 1997

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Armitage; Richard J.	Bainbridge Island	WA		
Fanslow, III; William C.	Federal Way	WA		
Longo; Dan L.	Kensington	MD		
Murphy; William J.	Frederick	MD		

US-CL-CURRENT: 424/144.1; 424/143.1, 424/153.1, 424/154.1, 424/155.1, 424/172.1, 424/173.1, 424/174.1, 514/2, 514/8

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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Term	Documents
CD40L.USPT,PGPB.	133
CD40LS.USPT,PGPB.	2
CD40.USPT,PGPB.	569
CD40S	0
LIGAND.USPT,PGPB.	34121
LIGANDS.USPT,PGPB.	27926
GP39.USPT,PGPB.	87
GP39S	0
ANTIBOD$	0
ANTIBOD.USPT,PGPB.	267
((CD40L OR CD40 ADJ LIGAND OR GP39)SAME (ANTIBOD$)SAME (LEUKEMIA$ OR LYMPHOMA$)).USPT,PGPB.	9

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LIGANDS.USPT,PGPB.	27926
GP39.USPT,PGPB.	87
GP39S	0
ANTIBOD$	0
ANTIBOD.USPT,PGPB.	267
. . . . .	
ANTIBOD$(ANTIBODY.PRODUCING).USPT,PGPB.	pickup term
((CD40L OR CD40 ADJ LIGAND OR GP39)SAME (ANTIBOD$)SAME (LEUKEMIA$ OR LYMPHOMA$)).USPT,PGPB.	9

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- EPO Abstracts Database
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- IBM Technical Disclosure Bulletins

Refine Search: `(cd40L or cd40 adj ligand or gp39)same (antibod$)same (leukemia$ or lymphoma$)` Clear

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DB Name	Query	Hit Count	Set Name
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L3: Entry 3 of 4 File: DWPI Mar 26, 2001

DERWENT-ACC-NO: 1999-229142
DERWENT-WEEK: 200161

TITLE: New humanized antibodies to human gp30

ABTX:
USE - The humanized antibodies can be used for the treatment of a disease treatable by modulating gp39 expression or inhibiting the gp39/CD40 interaction (claimed). They can be used for treating e.g. autoimmune diseases such as rheumatoid arthritis, psoriasis multiple sclerosis, diabetes, systemic lupus erythematosus and idiopathic thrombcytopenic purpura (ITP) or non-autoimmune conditions such as graft-versus-host disease (GVHD) or graft rejection, (claimed). They can also be used for the treatment of reversible obstructive airways disease, intestinal inflammations and allergies (e.g. coeliac disease, Crohn's disease and ulcerative colitis) and food-related allergies (e.g. migraine, rhinitis and eczema), transplant rejection, asthma, leukemia, or lymphoma. The antibodies can also be used as immunosuppressants, in particular during gene or cellular therapy. They may be used to inhibit humoral and cellular immune responses against viral vectors, e.g. retroviral vectors or adenoviral vectors. The use of such antibodies should enable such cells or vectors to be administered repeatedly, which will facilitate treatment of chronic diseases such as cancers and autoimmune diseases.

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L3: Entry 2 of 4 File: EPAB Aug 1, 1996

DOCUMENT-IDENTIFIER: WO 9623071 A2
TITLE: MONOCLONAL ANTIBODIES SPECIFIC FOR DIFFERENT EPITOPES OF HUMAN gp39 AND METHODS FOR THEIR USE IN DIAGNOSIS AND THERAPY

FPAR:
The present invention provides monoclonal antibodies, antigen binding fragment and recombinant binding proteins specific for human gp39. These antibodies are specific for at least 12 different epitopes on gp39. Hybridomas secreting specific antibodies which bind to these epitopes are also provided. Further, the present invention discloses the amino acid sequence of immunoglobulin light and heavy chain variable regions which bind to epitopes of gp39 and provide sFv and humanized antibodies which bind gp39. Also, provided are pharmaceutical compositions comprising the monoclonal antibodies, antigen binding fragments and recombinant binding proteins which bind gp39 and methods for using these compositions in diagnosing disease states, inhibiting B cell activation and for treating immunological disorders, such as autoimmune diseases, allergic responses, organ rejection and graft-versus-host disease. Antibodies of the present invention can also be used to image cells which express gp39 on their surface, such as tumor cells (e.g., lymphoma) and to target therapeutic agents to target cells.

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Search Results - Record(s) 1 through 4 of 4 returned.

☐ 1. Document ID: US 5876950 A

L3: Entry 1 of 4 File: EPAB Mar 2, 1999

PUB-NO: US005876950A
DOCUMENT-IDENTIFIER: US 5876950 A
TITLE: Monoclonal antibodies specific for different epitopes of human GP39 and methods for their use in diagnosis and therapy

PUBN-DATE: March 2, 1999

INVENTOR-INFORMATION:

NAME	COUNTRY
SIADAK, ANTHONY W	US
HOLLENBAUGH, DIANE L	US
GILLILAND, LISA K	US
GORDON, MARCIA L	US
BAJORATH, JURGEN	US
ARUFFO, ALEJANDRO A	US

INT-CL (IPC): A61K 39/395; C07K 16/28
EUR-CL (EPC): C07K014/705; C07K016/28

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Drawi Desc | Image

☐ 2. Document ID: WO 9623071 A2

L3: Entry 2 of 4 File: EPAB Aug 1, 1996

PUB-NO: WO0009623071A2
DOCUMENT-IDENTIFIER: WO 9623071 A2
TITLE: MONOCLONAL ANTIBODIES SPECIFIC FOR DIFFERENT EPITOPES OF HUMAN gp39 AND METHODS FOR THEIR USE IN DIAGNOSIS AND THERAPY

PUBN-DATE: August 1, 1996

INVENTOR-INFORMATION:

NAME	COUNTRY
SIADAK, ANTHONY W	US
HOLLENBAUGH, DIANE	US
GILLILAND, LISA K	GB
GORDON, MARCIA L	US
BAJORATH, JURGEN	US
ARUFFO, ALEJANDRO A	US
HARRIS, LINDA J	US

INT-CL (IPC): C12N 15/13; C07K 16/28; G01N 33/577; C07K 19/00; C12N 5/20; A61K 47/48; A61K 39/395; A61K 51/10
EUR-CL (EPC): C07K014/705; C07K016/28

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 3. Document ID: KR 2001023787 A, WO 9912566 A1, AU 9895652 A, NO 200001104 A, EP 1011725 A1, CN 1278736 A

L3: Entry 3 of 4 File: DWPI Mar 26, 2001

DERWENT-ACC-NO: 1999-229142
DERWENT-WEEK: 200161

TITLE: New humanized antibodies to human gp30

INVENTOR: BLACK, A; HANNA, N ; NEWMAN, R A ; PADLAN, E A

PRIORITY-DATA: 1997US-0925339 (September 8, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
KR 2001023787 A	March 26, 2001		000	A61K039/395
WO 9912566 A1	March 18, 1999	E	121	A61K039/395
AU 9895652 A	March 29, 1999		000	
NO 200001104 A	May 8, 2000		000	C12P000/00
EP 1011725 A1	June 28, 2000	E	000	A61K039/395
CN 1278736 A	January 3, 2001		000	A61K039/395

INT-CL (IPC): A61K 39/395; C07H 21/04; C07K 16/00; C07K 16/18; C07K 16/28; C12N 5/10; C12N 15/13; C12P 0/00; C12P 21/08

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw Desc | Image

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☐ 4. Document ID: US 5674492 A

L3: Entry 4 of 4 File: DWPI Oct 7, 1997

DERWENT-ACC-NO: 1997-502273
DERWENT-WEEK: 199746

TITLE: Treating or preventing neoplastic disease associated with CD40-expressing cells - particularly B-cell lymphoma, by administration of CD40-binding protein, preferably antibody or soluble CD40-ligand

INVENTOR: ARMITAGE, R J; FANSLOW, W C ; LONGO, D L ; MURPHY, W J

PRIORITY-DATA: 1994US-0360923 (December 21, 1994), 1993US-0172664 (December 23, 1993)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 5674492 A	October 7, 1997		021	A61K039/395

INT-CL (IPC): A61K 35/12; A61K 38/02; A61K 39/395

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Term	Documents
CD40L.DWPI,EPAB,JPAB.	48
CD40LS	0
CD40.DWPI,EPAB,JPAB.	184
CD40S	0
LIGAND.DWPI,EPAB,JPAB.	22490
LIGANDS.DWPI,EPAB,JPAB.	10051
GP39.DWPI,EPAB,JPAB.	37
GP39S	0
ANTIBOD$	0
ANTIBOD.DWPI,EPAB,JPAB.	48
((CD40L OR CD40 ADJ LIGAND OR GP39)SAME (ANTIBOD$)SAME(LEUKEMIA$ OR LYMPHOMA$)).JPAB,EPAB,DWPI.	4

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1) brugnoni et al. haematologica 80 / 5 : 440 -442 !(995)

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3) schattner et al. leukemia and lymphoma 37 / 5 - 6 : 461 - 472 (2000)

4) dilloo et al. blood 90 (5) : 1927 - 1933 (1997)

5) kneitz et al. leukemia 13 (1) : 98 - 104 (1999)

6) wirerda et al. blood 94 (10 suppl 1 part 1) : page 602 a (nov. 15, 1999)

7) laytragoon-lewin medical oncology 15 / 1 : 15 - 19 (1998)

8)gruss et al. leukemia and lymphoma 24 / 5-6 : 393 - 422 (1997)

9) planken et al. leukemia and lymphoma 22 (3-4) : 229 - 235 (1996)

10) gruss et al. annals of hematology 73 (suppl 2) : page A131 (1996)

11) schattner et al. blood 88 (10 suppl 1 part 1-2): page 218 B (1996)

12) dilloo et al. blood 88 (10 suppl 1 part 1-2) : page 275A (1996)

13) planken et al. british journal of haemotology 95 (2) : 319 - 326 (1996)

14) nathalie et al. blood 87 (12) : 5162 - 5170 (1996)

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Sent: Tuesday, November 13, 2001 3:00 PM
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2) younes et al. british journal of haematology 100 / 1 : 135 - 141 (1998)

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5) kneitz et al. leukemia 13 (1) : 98 - 104 (1999)

6) wirerda et al. blood 94 (10 suppl 1 part 1) : page 602 a (nov. 15, 1999)

7) laytragoon-lewin medical oncology 15 / 1 : 15 - 19 (1998)

8)gruss et al. leukemia and lymphoma 24 / 5-6 : 393 - 422 (1997)

9) planken et al. leukemia and lymphoma 22 (3-4) : 229 - 235 (1996)

10) gruss et al. annals of hematology 73 (suppl 2) : page A131 (1996)

11) schattner et al. blood 88 (10 suppl 1 part 1-2): page 218 B (1996)

12) dilloo et al. blood 88 (10 suppl 1 part 1-2) : page 275A (1996)

13) planken et al. british journal of haemotology 95 (2) : 319 - 326 (1996)

14) nathalie et al. blood 87 (12) : 5162 - 5170 (1996)

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2) younes et al. british journal of haematology 100 / 1 : 135 - 141 (1998)

3) schattner et al. leukemia and lymphoma 37 / 5 - 6 : 461 - 472 (2000)

4) dilloo et al. blood 90 (5) : 1927 - 1933 (1997)

5) kneitz et al. leukemia 13 (1) : 98 - 104 (1999)

6) wirerda et al. blood 94 (10 suppl 1 part 1) : page 602 a (nov. 15, 1999)

7) laytragoon-lewin medical oncology 15 / 1 : 15 - 19 (1998)

8)gruss et al. leukemia and lymphoma 24 / 5-6 : 393 - 422 (1997)

9) planken et al. leukemia and lymphoma 22 (3-4) : 229 - 235 (1996)

10) gruss et al. annals of hematology 73 (suppl 2) : page A131 (1996)

11) schattner et al. blood 88 (10 suppl 1 part 1-2): page 218 B (1996)

12) dilloo et al. blood 88 (10 suppl 1 part 1-2) : page 275A (1996)

13) planken et al. british journal of haemotology 95 (2) : 319 - 326 (1996)

14) nathalie et al. blood 87 (12) : 5162 - 5170 (1996)

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Article title	Programmed cell death: The influence of CD40, CD95 (Fas or Apo-I) and their ligands
Article identifier	0736011898000713
Authors	Laytragoon-Lewin_N
Journal title	Medical Oncology
ISSN	0736-0118
Publisher	Macmillan
Year of publication	1998
Volume	15
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Abstract# 2678

EFFECT OF CD40 ACTIVATION ON CYTOTOXIC T LYMPHOCYTE LYSIS OF HUMAN CHRONIC LYMPHOCYTIC LEUKEMIA B CELLS.

P. Chu*,[1] W. G. Wierda,[2] L. Z. Rassenti,[2] T. J. Kipps.[1,2] *[1]Biomedical Sciences Graduate Program; [2]Division of Hematology/Oncology, School of Medicine, UC San Diego, La Jolla, CA.*

Engagement of CD40 on chronic lymphocytic leukemia (CLL) B cells induces or upregulates expression of immune co-stimulatory molecules, such as CD80, CD86, CD70, and CD54. Consequently, CD40-activated CLL-B cells become highly effective stimulators of T cells in mixed lymphocyte reactions and can induce even autologous T cells to generate CLL-specific cytotoxic T lymphocytes (CTL) *in vitro* (*J. Clin. Invest.* 101:1133, 1998). CLL B cells that undergo CD40-ligation also are induced to express CD95 (Fas), a receptor that can trigger apoptosis when ligated by its ligand or by CD95 mAbs. Despite this, CD40-activated CLL cells are resistant to Fas-mediated apoptosis. This is secondary in part to CD40-induced upregulation of FLIP, a cytosolic protein that can compete with caspase-8/FLICE for binding to the FADD/MORT1 death domain of the Fas-receptor, thereby precluding activation of downstream caspases in the Fas-induced apoptotic pathway. We examined whether CD40-activated CLL cells also were resistant to CTL-mediated apoptosis. For this, T cells were isolated from the blood of normal donors and cultured in AIM-V media with recombinant human IL-2 (50U/mL) and mitomycin-C-treated CLL B cells that had been freshly activated for 48 hours with an agonistic form of soluble CD40-ligand. The effector T cells were harvested and tested for their ability to induce apoptosis of resting or CD40-activated CLL target cells in a CTL assay developed in our laboratory (*Cell. Immunol.* 195:43, 1999). We found that resting or CD40-activated CLL cells were equally sensitive to CTL-mediated killing. At effector:target cell (E/T) ratios of 5:1 (n=4), over 80% of the target cells from either population were induced to undergo apoptosis within the 4 hour assay. Moreover, analyses of CTL-killing at various E/T ratios yielded identical results for the two target-cell populations. In contrast, neither of the target-cell populations underwent apoptosis in the absence of added effector cells. Furthermore, despite expressing CD95, the CD40-activated CLL target cells again were noted to be resistant to apoptosis induced by CH11, an IgM CD95 mAb, suggesting that the mechanism of CTL killing most likely involved the perforin/granzyme-mediated pathway. Consistent with this, we noted that CTL killing of CLL target cells could not be inhibited with inhibitors of caspases involved in the Fas-induced apoptotic pathway (e.g. N-carbobenzoxy-Val-Ala-Asp fluoromethyl ketone (z-VAD-fmk)). Also, pre-incubation of the effector T cells with anti-Fas-ligand mAb NOK-3 failed to inhibit their subsequent ability to induce apoptosis of the CLL target cells. On the other hand, CTL activity could be inhibited by W6/32, a mAb specific for a non-polymorphic epitope of HLA class I molecules, or by inhibitors of target-cell/effector-cell conjugate formation, e.g. ethylene-glyco-tetra-acetic acid or Cytochalasin B. We conclude that CD40-activation does not reduce the sensitivity of CLL cells to Fas-independent CTL-mediated apoptosis.

Abstract# 2679

IMPROVED THERAPEUTIC OUTCOME FOLLOWING COMBINATION IMMUNOGENE VACCINATION THERAPY IN MURINE MYELOMA.

Zhi Hua Li*,[1] Saul Mandelbaum*,[1] Teresa Hawley*,[2] Robert G. Hawley,[2] A. Keith Stewart.[1] *[1]Oncology Research, Toronto General, Toronto, ON, Canada; [2]Holland Laboratories, American Red Cross, Rockville, MD.*

Accumulating evidence suggests that genetic immunotherapy may assist in the management of minimal residual myeloma. In animal models ectopically introducing immune stimulatory genes into whole myeloma cells can result in the rejection by host animals of gene modified cells, protection of the host from subsequent parental tumor challenge and occasionally rejection of pre-established tumor. To further explore this issue IL- 6 dependent B9BM1 murine "myeloma" cells were engineered using MSCV based retroviral vectors to express GM-CSF (70 ng/24 hrs), soluble Flt3L (200 ng /24 hours) or membrane bound Flt3L (85% positive). Mice challenged with viable B9BM1-sFlt3L cells developed tumors at the same speed as controls. In these mice splenomegaly was noted, 800-1600 ng of Flt3L was present in serum and splenic cells were 44% CD11c, MHCII positive. Unirradiated B9BM1-GM-CSF cells also grew and serum contained 20-30ng/ml of GM-CSF. Thus systemic production of Flt3L or GM-CSF was inadequate to prevent tumor growth. B9BM1 cells engineered to express IL-12 and CD80 did not grow after s.c. or i.v. injection. Irradiated sFlt3L, mbFlt3L, GM-CSF and unirradiated IL-12/CD80 expressing B9BM1 cells each conferred some protective immunity when used individually as a vaccine prior to s.c. but not i.v. parental tumor challenge. GM-CSF expressing B9BM1 cells were most effective as a single gene preventative vaccine although significant activity of mbFlt3L was also observed. In contrast,the combination of GM-CSF, Flt3L, IL-12 and CD80 was 100% effective against s.c. challenge while all other combinations of agents were only partially protective. No single gene expressing,, irradiated cell vaccine inhibited growth of established myeloma and IL12.CD80 expressing cells although significantly delaying myeloma growth did not ultimately eradicate disease. In contrast 5 of 17 (29%) mice subjected to combination therapy were completely protected from further growth of established tumor. Enhanced splenic lymphocyte proliferation and CTL activity was observed for both GM-CSF vaccine treated or for the combination gene vaccinated mice. Protection by combination immunogene therapy was completely abrogated in a SCID model and when cells were isolated in a Theracyte™ immunoencapsulation device prior to implantation in mice. In summary, irradiated myeloma cells engineered to secrete GM-CSF are superior to cells expressing Flt3L and to our previous gold standard of IL-12 in combination with CD80. Furthermore, we demonstrate that use of GM-CSF, Flt3L, IL-12 and CD80 in concert is synergistic, is superior to use of any single gene products used in isolation and that the positive treatment effect of combination gene therapy is T cell mediated and may require cell-cell contact.

Abstract# 2680

ABNORMAL CD30 AND CD153 EXPRESSION AND INTERACTION IMPAIRS CD154:CD40-DEPENDENT IMMUNOGLOBULIN CLASS SWITCHING AND ANTIBODY PRODUCTION IN CHRONIC LYMPHOCYTIC LEUKEMIA.

Andrea Cerutti*,[1] Carmela Gurrieri*,[1] Shefali Sha*,[1] Elaine Schattner,[1] Nicholas Chiorazzi,[2] Paolo Casali*.[1] *[1]Department of Pathology and Department of Medicine, Weill Medical College of Cornell University, New York, NY; [2]Department of Medicine, North Shore University Hospital, Manhasset, NY.*

Chronic lymphocytic leukemia (CLL) is characterized by the clonal expansion of naïve-like B cells that usually express surface IgM and IgD and only rarely undergo switching to IgG or IgA. CLL is also associated with impaired IgG, IgA, and IgE production by residual normal B cells, a defect that ultimately leads to hypogammaglobulinemia and increased susceptibility to bacterial infections. As CD154:CD40 T:B cell interaction is critical for Ig class switching and production to occur, we analyzed the regulation of class switch DNA recombination (CSR) and Ig production in IgD$^+$ CLL B cells exposed to CD154 and appropriate cytokines. In addition, we evaluated the ability of activated T cells from CLL patients to induce CSR and Ig secretion in normal naïve IgD$^+$ B cells.

Upon exposure to CD154 and IL-4, CLL cells up-regulate the binding of NF-κB/Rel and STAT-6 to downstream C_H germline gene promoters, induce downstream I_H-C_H germline transcripts, up-regulate the expression of the SWAP-70 CSR-associated gene, and undergo CSR to Cγ, Cα, or Cε. When exposed to IL-2 and IL-10, these induced CLL B cells express Blimp-1 (a positive regulator of Ig secretion), up-regulate the plasma cell-associated markers CD38 and CD138 (syndecan-1), accumulate cytoplasmic Igs, and secrete variable amounts of IgM, IgG, IgA, or IgE.

Compared to naïve B cells, unstimulated CLL B cells express normal levels of surface CD40, but higher levels of surface CD153 (a CD40-inhibitory molecule) and nuclear BSAP (an inhibitor of Ig secretion). Compared to similarly induced B cells, CD154 and cytokine-induced CLL B cells express decreased levels of Blimp-1 transcripts, display increased levels of nuclear BSAP, and secrete smaller amounts of Igs. In both CD40-activated naïve B cells and CLL B cells, CD153 engagement by T cell CD30 inhibits CSR, Ig secretion, and Blimp-1 expression, but increases expression of nuclear BSAP.

Compared to normal T cells, CD3 and CD28-activated T cells from CLL patients present decreased expression of CD154, increased expression of CD30 (the CD153 counter-receptor), and reduced ability to induce Ig class switching and secretion in normal naïve B cells. Finally, purified CLL CD30$^+$ T cells inhibit both CSR and Ig secretion in normal naïve B cells induced by exogenous CD154 and cytokines.

These findings formally demonstrate that CLL B cells can undergo efficient CSR to downstream isotypes when exposed to appropriate stimuli. They also suggest that the ineffective CSR characteristic of both neoplastic and normal B cells in CLL patients stems from a profoundly altered CD30:CD153 expression and interaction.

ORAL SESSION I

Abstract# 2681

A PHASE I STUDY OF CD154 (CD40-LIGAND) GENE THERAPY FOR CHRONIC LYMPHOCYTIC LEUKEMIA.

W. G. Wierda,[1] L. Z. Rassenti,[1] M. J. Cantwell*,[1] S. J. Woods*,[1] T. J. Kipps.[1] *[1]Division of Hematology/Oncology, UCSD Human Gene Therapy Program, Dept. of Medicine, UCSD School of Medicine, La Jolla, CA.*

The leukemia B cells of patients with chronic lymphocytic leukemia (CLL) can be transduced to express recombinant CD154 (CD40-ligand) using high-titer replication-defective adenovirus vector (Ad-CD154). Unlike CLL-B cells transfected with control adenovirus vectors, Ad-CD154-infected CLL-B cells become highly effective stimulators of autologous T cells in mixed lymphocyte reactions and can even induce autologous T cells to generate CLL-specific cytotoxic T lymphocytes *in vitro* (J. Clin Invest. 101:1133, 1998). Moreover, Ad-CD154-infected CLL cells can induce phenotypic changes on bystander non-infected CLL-B cells that render these cells also more effective at presenting antigens to T cells. Here we report on a phase I dose-escalation gene therapy trial in which eleven CLL patients received a one-time intravenous infusion of Ad-CD154-infected autologous leukemia cells. Two subjects (pilot group) received $3x10^8$ leukemia cells of which <8% expressed CD154 transgene. These subjects did not experience any toxicity or substantial clinical response. Three subjects per group each received $3x10^8$ (group 1), $1x10^9$ (group 2), or $3x10^9$ (group 3) autologous Ad-CD154-infected CLL-B cells. The mean percent cells expressing the CD154 transgene was 49%±12% (±S.D.) for groups 1-3. The infusions were well tolerated with no immediate toxicity. Patients generally experienced fever, fatigue, and anorexia within 12 hours of the infusion. Less common clinical toxicities included nausea, myalgia, arthralgia, and diarrhea. Laboratory toxicities included elevated transaminases and thrombocytopenia. Both clinical and laboratory abnormalities were transient and resolved within a few days after the infusion. However, significant clinical responses were observed. Increased expression of CD54, CD95, CD80, and CD86 were induced *in vivo* on bystander leukemia cells 1-2 days after treatment. Measurable increases in plasma concentrations of IFN-γ, IL-6, and IL-12 were detected within 1-2 days after infusion. Increases in absolute T cell counts (mean=243%±154%) were observed in the blood of all subjects within 1-4 weeks after treatment. Significantly, patients in groups 1-3 experienced an average reduction in absolute lymphocyte counts of 40%±21% (±S.D.) (median=43%) and an average decrease in lymph node mass of 70%±19% (±S.D.) (median=77%) within 1-4 weeks after treatment. Overall, we did not observe a clear dose-response relationship with respect to toxicity, biologic activity, or clinical response. This study indicates that infusion of autologous AdCD154 transduced CLL B cells is well tolerated and may have significant biologic activity in the treatment of this disease.

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1087 530-II

THE COMBINATION OF THE T CELL CHEMOKINE LYMPHOTACTIN AND THE T CELL GROWTH FACTOR INTERLEUKIN-2 GENERATES A POTENT ANTI-TUMOR RESPONSE. D. Dilloo,[1]* K. Bacon,[2]* W. Zhong,[1]* St. Burdach,[3] A. Zlotnik,[2]* M. Brenner,[1] St. Jude Children's Research Hospital, Memphis TN[1], DNAX Research Institute, Palo Alto, CA[2], Heinrich-Heine University Dusseldorf, Germany[3]

Specific antitumor responses are generated when the relevant antigens are presented to T cells with the appropriate receptor specificity. If the numbers of T lymphocytes encountering these immunogenic stimuli were increased, there should be a corresponding increase in the probability of generating a successful antitumor response. We tested this prediction using a murine model and a recently discovered T-cell chemokine, lymphotactin (LTN), given with or without the T cell stimulatory cytokine interleukin-2 (IL-2). In mice co-injected with A20 tumor cells and fibroblasts genetically modified to secrete LTN, there was increased T-cell infiltration of the tumor cells, but no appreciable effect on tumor development. However, combined delivery of IL-2-secreting fibroblasts with cells modified to produce LTN substantially enhanced antitumor responses, compared to results obtained with LTN or IL-2 alone ($p<0.0005$). This chemokine/cytokine combination also suppressed the growth of pre-existing tumor ($p<0.02$) and significantly improved survival. While LTN alone induced infiltration only of CD4+ cells, and IL-2 alone induced limited infiltration of both CD4 and CD8 positive cells, the combination of IL-2 and LTN lead to extensive and uniform infiltration with both CD4+ and CD8+ T lymphocytes. In vivo depletion of either CD4+ or CD8+ cells abrogated the protective effects of the LTN/IL-2 combination on tumor growth and murine survival confirming the importance of T cells in the anti-tumor activity of LTN and IL-2. In addition, NK cells seem to contribute to the LTN -mediated anti-tumor response, as a protective effect of both LTN alone and the LTN/IL-2 combination could be observed in nude mice and was abrogated by NK cell depletion. Hence the chemokinetic effects of LTN extends beyond the T cell compartment. Attraction and expansion of cytotoxic effectors by administration of a chemokine and cytokine combination potentiates antitumor responses in vivo, suggesting a general strategy for the improvement of cancer immunotherapy.

1088 531-II

CD40 LIGAND ACTS AS A Co-STIMULATOR MOLECULE FOR THE GENERATION OF AN ANTI-LEUKEMIC IMMUNE RESPONSE AND ITS ACTIVITY IS ENHANCED BY INTERLEUKIN-2 (IL-2). D. Dilloo*, M. Brown*, W. Zhong*, M. Holladay* and M. Brenner, St. Jude Children's Research Hospital, Memphis TN.

Leukemic cells may escape immune surveillance by failing to express T-cell co-stimulatory molecules. CD40 ligand (gp39) is a cell surface antigen that can act as a co-stimulator molecule after binding to its counter receptor CD40 on T and B cells. This activity led us to investigate whether transgenic expression of the CD40 ligand (CD40L) in the presence of malignant cells can induce systemic anti-leukemic activity. We initially used non-immunogenic A20 tumor cells, a CD40 positive B cell leukemia line. Transgenic expression of CD40L at one tumor site significantly delayed growth of pre-existing A20 tumor at a distal site ($p<0.05$ compared to *neo* transduced control cells). Because CD40L directly upregulates T cell function, we analyzed tumor growth and survival after combining this T cell co-stimulator molecule with the T cell growth factor IL2. Mice receiving cells expressing both IL2 and CD40L produced the greatest anti tumor response ($p<0.005$ in comparison to IL2 or CD40L alone), and had the best survival at day 45 (6/7 mice alive in the CD40L+IL2 group versus 0/7). The CD40L effect required an intact T lymphocyte and NK cell system, being abrogated by antibody depletion of each subset. In contrast, the effects did not require the tumor cell itself to express the CD40 receptor. CD40 positive A20 cells certainly respond directly to CD40L. We found that expression of co-stimulatory molecules such as B7.1, and Class I/II MHC antigens was upregulated in the presence of CD40L, favoring antigen presentation of tumor antigens by malignant cells. Additionally, CD40L upregulates A20 cell expression of Fas and increases apoptosis, an effect that will favor tumor antigen uptake and presentation by professional antigen presenting cells. However, none of these effects are obligatory for the anti-tumor effects of CD40L, since transgenic CD40L expression produces identical anti-tumor effects when we substitute CD40 negative WEHI-3 myeloid leukemia cells in our murine model. Hence the primary activity of CD40L is to recruit CD4/CD8 and NK cell responses, so that it should be a generally effective immunostimulatory molecule for the generation of leukemia "vaccines". Its effects will likely be enhanced by IL-2.

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MARKING OF CANINE HEMATOPOIETIC PROGENITORS IN CYTOKINE STIMULATED BONE MARROW WITH RETROVIRUSES CONTAINING THE IL2RG GENE. Todd Whitwam[1]*, Nancy E. Seidel[1]*, Mark E. Haskins[2]*, Stacie M. Anderson[1]*, Paula S. Henthorn[2]*, David M. Bodine[1], Jennifer M. Puck[1]*. Laboratory of Gene Transfer, National Center for Human Genome Research, NIH[1], and School of Veterinary Medicine, Univ. of Pennsylvania[2].

A naturally occurring deficiency of canine interleukin receptor common gamma chain (γc) (IL2RG) causes X-linked severe combined immune deficiency in the dog. We hypothesized that this animal model might be useful for evaluating strategies to treat X-linked SCID, the most common cause of human SCID. We created two high titer amphotropic retroviral vectors to evaluate retrovirus mediated gene transfer into hematopoietic stem cells as a treatment for X-linked SCID. MGNEO uses the MoMLV LTR as a promoter for IL2RG and contains the dominant selectable marker NEO which uses an internal ribosome entry site (IRES) for translation. HGMDR uses HaMSV LTR as a promoter for IL2RG and contains the selectable marker MDR linked to an IRES. The titer of MGNEO on 3T3 cells is ~1.3×10^7cfu/ml. HGMDR's titer is ~2.0×10^7cfu/ml. We have previously shown that pretreatment of primates with G-CSF and SCF 14 days before bone marrow harvest results in more efficient transduction of HSC when using amphotropic retroviruses (Dunbar et al, *PNAS* in press). In this study, bone marrow cells (BMC) were retrieved from the long bones of a normal donor ten days after a four day regimen of cytokine treatment (canine stem cell factor (cSCF) 25μg/kg/ day & canine G-CSF 10μg/kg/ day) used to increase the number of hematopoietic stem cells (HSC) in the bone marrow. The BMC were transduced with either MGNEO or HGMDR by exposing them to four daily changes of supernatant from MGNEO or HGMDR producer cells in the presence of polybrene, cSCF and IL-6. After transduction, BMC were infused into a normal MHC matched, sublethally irradiated (200cGy TBI) 4kg puppy. Human IL2RG, from both the MGNEO and HGMDR vectors, was detected by PCR in ~30% of peripheral blood cells through six weeks, and in the bone marrow at five weeks after infusion. Simultaneous FACS analysis indicated the presence of human γc in 30% of the recipient's peripheral blood and bone marrow cells. The demonstration of human γc gene transfer and expression in hematopoietic cells of a normal dog, predicts that such treatment will correct the γc deficiency in X-linked SCID dogs as well. These studies should offer a model for the treatment of human patients affected with X-linked SCID.

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INFLUENCE OF GENE MODIFIED (IL-7, IL-4 AND B7) TUMOR CELL VACCINES ON TUMOR ANTIGEN PRESENTATION. S. Cayeux,* G. Richter,* G. Noffz,* Bernd Dörken* and Th. Blankenstein* (intr. by A. Pezzutto) Dept. of Hematology, Oncology and Tumorimmunology, Robert-Rössle Klinik, Virchow Klinikum, Humboldt University, Berlin and Max-Delbrück-Center for Molecular Medicine, Berlin, Germany

We have previously shown that tumor cells genetically modified to coexpress IL-4 or IL-7 and B7.1 have increased immunogenicity and provide vaccines superior to single gene transfectants or tumor cells/adjuvant mixture. Tumor antigens can be presented either directly by tumor cells or be represented by host APC (cross-priming). Here we asked whether B7.1 and IL-7 or IL-4 improved in an additive fashion one pathway of antigen presentation or complement each other by improving preferentially different pathways of antigen presentation. We used two mouse tumor cells, one syngeneic to H-2d BALB/c mice (TS/A) and its -IL7, -B7 and -IL7/B7 transfectants and another syngeneic to H-2b C57BL/6 mice (MCA205) and its -IL-4 and -B7 transfectants. All the above cell lines were transfected to express the surrogate antigen β-galactosidase (*β- gal)* which has a predominant MHC class I epitope in H-2d (BALB/c) mice, β-gal (876-884) presented by H-2Ld and a predominant epitope in H-2b (C57BL/6) mice, β-gal (497-504) presented by H-2Kb. After immunization of (C57BL/6 x BALB/c)F1 (H-2bxd) mice with βgal positive H-2d transfectants, we could demonstrate that i) both IL-7 and B7.1 augmented cross-priming and rejection of H-2b challenge tumor cells.ii) similarly, immunization with B7.1 or IL-4 β-gal positive H-2b transfectants enhanced cross-priming and rejection of H-2d tumor cells. iii) however, direct antigen presentation by tumor cells was enhanced only by B7.1 and not IL-7. For this study, H-2b (C57BL/6) nu/nu mice were reconstituted with (C57BL/6 x BALB/c)F1 (H-2bxd) lymphocytes, immunized with H-2d transfectants and challenged with H-2d tumor cells. Since host APCs are H-2b, suppression of H-2d challenge tumor growth was exclusively the result of antigen presentation by H-2d tumor cells used for immunization. In conclusion, several cytokines (GM-CSF, IL-3 and here IL-7 and IL-4) and B7 have been shown to increase cross-priming but B7 additionally enhanced direct priming. This may explain why cytokine/B7 transfected tumor cells show in our hands the strongest vaccine effect